

A clinical trial of a microcrystalline cellulose topical nasal spray on the acute response to allergen challenge

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ABSTRACT

Background: Allergic rhinitis is a common disorder that leads to a negative impact on quality of life. Multiple options are available for treatment of the symptoms, but preventing the reaction should be an effective strategy.

Objective: We tested a nasal spray that contained microcrystalline cellulose designed to limit airborne allergens from penetrating the nasal mucosa (nasal blocker) and, therefore, prevent the initiation of the allergic reaction.

Methods: We performed a randomized, double-blind, placebo-controlled, two-way crossover clinical trial with 20 subjects who had a history of seasonal grass and/or ragweed allergy symptoms. Each subject underwent two separate nasal challenges with antigen (provocations) after application of the investigational product or placebo to both nostrils. The allergen was delivered into one nostril at a time and was administered at 2-hour intervals (identified as challenge 1 and challenge 2). We assessed peak nasal inspiratory flow and total nasal symptoms as well as the number of sneezes recorded at both 15-minute and 1-hour intervals after challenge 1 and, later, challenge 2. After a washout period, the subjects returned to undergo the alternate therapy.

Results: There was a significant overall decrease in peak nasal inspiratory flow after both treatments (investigational product, $p = 0.005$; placebo, $p = 0.001$), but, when the average of the change from baseline in peak nasal inspiratory flow was compared with the baseline, the results showed no significant differences between the groups ($p = 0.31$). Similar results were obtained for total nasal symptoms.

Conclusion: The investigational product did not prove to be significantly better than placebo in treating seasonal allergic rhinitis symptoms.

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Allergic rhinitis is a common disease, estimated to affect 20% of Americans and causes significant decreases in patients' quality of life.¹ The symptomatic response to allergen exposure by patients with allergic rhinitis is characterized by an immunoglobulin E-mediated inflammatory mechanism.² When allergen contacts the nasal mucosa of individuals who are sensitized, an immediate reaction is triggered and is characterized by the secretion of histamine, leukotrienes, and other mediators from mast cells; the stimulation of neural reflexes; and changes in the vasculature of the nose.² This response generates the common symptoms characteristic of the disease, including sneezing, rhinorrhea, nasal itching, and nasal congestion as well as ocular symptoms, such as itchy and watery eyes.³

One strategy for treating allergic rhinitis is to block pollen from contacting the nasal mucosa. Several pollen blocker products exist on the market (e.g., Nasal Guard, a gel approved in the United States by the U.S. Food and Drug Administration), which aims at relieving allergy symptoms by blocking allergens from contacting the nasal mucosa.⁴ One potential blocker, a cream, has been studied in a double-blind, randomized, placebo-controlled, crossover study.⁵ The study took place at two centers located in Germany and Russia, and enrolled 91 patients with seasonal or perennial allergic rhinitis. The subjects were randomly assigned to one of two groups, each received either a pollen blocker cream ($n = 43$) or a placebo gel ($n = 48$). The blocker cream was significantly more effective than placebo in reducing the typical symptoms of allergic

rhinitis in response to nasal challenge with allergen.⁵ Another study, performed in China, showed similar beneficial results of a pollen blocker cream in a clinical trial that involved patients with perennial allergic rhinitis.⁶

OBJECTIVES

We investigated the efficacy of a novel agent, classified as a class II medical device, administered *via* metered-dose nasal spray, and intended as a preventive strategy for limiting airborne allergens from contacting the nasal mucosa, thereby decreasing the severity of allergic-rhinitis symptoms. We hypothesized that application of this spray would be more effective than placebo in controlling nasal symptoms induced by nasal allergen challenge.

METHODS

Study Design

We performed a randomized, double-blind, placebo-controlled, two-way crossover trial. A total of 20 adult subjects with a history of seasonal grass and/or ragweed allergy symptoms participated in the study. To be included, the participants had to be outside their relevant allergy season and, therefore, be symptom-free. Initial screening included an allergy questionnaire that assessed nasal symptoms and a skin-prick test result that confirmed grass or ragweed allergy. Screening nasal challenge with antigen was then performed with the use of filter paper disks applied to the anterior portion of the nasal septum, as previously described.⁷ The challenge involved the application of diluent for the allergen extracts, followed by three increasing doses of allergen. The dose of allergen that resulted in a positive response was used during visits 2 and 3. A positive response was defined as having an increase of ≥ 4 units in the severity of total nasal symptoms (sneezing, itchy nose, runny nose, and nasal congestion) after allergen compared with the response to the diluent.

The subjects who met the above inclusion criteria were then randomized to receive nasal spray treatment with either placebo or the investigational product. The crossover design served to enhance the innate comparability of subjects (*i.e.*, each subject served

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as his or her control, thereby reducing intersubject variability). A 14-day washout period was incorporated into the study design so that carryover effects from one challenge to the next were minimized. During visit 2, we first performed diluent challenge and 15 minutes later recorded the number of sneezes, symptoms, and measured peak nasal inspiratory flow (PNIF). Subsequently, and under controlled and blinded conditions, each subject received a one-time dose of two sprays (50 μ L per spray for a total of 100 μ L) of investigational product or placebo in each nostril. Ten minutes later, allergen challenge was performed in the left nostril (challenge 1). A similar challenge with allergen was also performed 2 hours later in the right nostril (challenge 2) as a test for the duration of the putative protective effect. Fifteen minutes and 1 hour after each of these challenges, sneezes were counted and nasal symptoms were recorded. PNIF was measured only at the 15-minute time point after each challenge. The subjects returned to the laboratory 14 days later (washout) for their third visit, once more undergoing a similar assessment after receiving the alternate therapy.

The primary goal of our study was to measure the relative change from diluent challenge for the total nasal symptom score (TNSS) at predefined intervals: 15 minutes and 1 hour after the first allergen challenge, which was performed in the left nostril (challenge 1), and again 15 minutes and 1 hour after allergen challenge in the right nostril (challenge 2). This study was approved by the institutional review board of the University of Chicago; all the participants provided written informed consent.

Subjects

Twenty healthy adults between the ages of 18 and 55 years with seasonal allergic rhinitis were enrolled in the study. All the subjects demonstrated a positive skin-prick test to either grass or ragweed, a medical history of seasonal allergic rhinitis, and a positive nasal response to allergen challenge (for either grass or ragweed), as defined by an increase in TNSS of ≥ 4 compared with the postdiluent symptoms. Exclusion criteria were the following: a history of any disease other than allergic rhinitis and mild asthma; use of corticosteroids within 4 weeks or antihistamines within 1 week before screening; upper respiratory infection < 14 days before screening; a history of structural nasal abnormalities or nasal polyps on examination; frequent nose bleeds; a history of receiving immunotherapy within 2 years before screening; current smoker or recent ex-smoker, defined as history of smoking within 2 months before screening; and pregnancy or lactation in women.

Treatment

The subjects who met inclusion criteria at visit 1 were randomized to receive nasal spray treatment with either placebo or the investigational product at visit 2. The investigational product itself was an allergen blocker in nasal spray form, a clear or translucent liquid with menthol and with microcrystalline cellulose as the active ingredient. The active spray formulation contained the following: benzyl alcohol National Formulary (N.F.) dibasic sodium phosphate United States Pharmacopeia (U.S.P.) (anhydrous), edetate disodium U.S.P. (dihydrate), fragrance (Cool Vapor Rush SN914680, Cool Vapor, St. Louis, MO), glycerin U.S.P., menthol U.S.P., microcrystalline cellulose and carboxymethylcellulose, sodium N.F. (Avicel RC-591, FMC Corporation, Philadelphia, PA), monobasic sodium phosphate U.S.P. (anhydrous), polyethylene glycol 400 N.F., polysorbate 80 N.F. (Tween 80V Pharma, Corda International/PLC, Edison, NJ), povidone U.S.P. (Plasdone K-29/32, Ashland, Covington, KY), and purified water U.S.P. The placebo was a nasal spray formulation, outwardly indistinguishable from the investigational product, including its color, menthol odor, and the inclusion of components from the investigational product, except for the active ingredient. Both the investigational product and placebo were packaged within the same three-piece, metered,

liquid, spray-pump bottle with a snap-on cap, with labeling blinded for the study staff.

Symptom Score and Sneeze Number

Severity of sneezing, rhinorrhea, nasal congestion, and itchy-nose symptoms were recorded on a scale from 0 to 3 (0, no symptoms; 1, mild; 2, moderate; and 3, severe). The number of sneezes subsequent to both early and late challenges was also counted.

PNIF

PNIF (in L/min) was measured objectively with an In-Check Peak and Inspiratory Flow Meter (Ferraris Medical Inc, Orchard Park, NY). The highest of three successive measurement values was recorded. The change from baseline in PNIF was measured as an exploratory end point. The sham assessment for PNIF was obtained after diluent challenge and before administration of the investigational product or placebo.

Statistical Analysis

The primary outcome measure was the change from baseline in TNSS at 15 and 60 minutes for first and second challenges. Secondary outcome measures were the changes from baseline in sneezes and PNIF. PNIF and symptom score data were not normally distributed and were analyzed with the use of nonparametric statistics. We first examined the overall change within each treatment arm by the Friedman analysis of variance, and, if there was a significant effect, then we compared the postallergen responses to diluent by using the Wilcoxon signed rank test. We then calculated the change from the diluent response at the two time points for each challenge and each treatment arm, and compared that response between active and placebo treatments by using the Wilcoxon signed rank test. All data are reported as median (range).

The sample size was determined by a power calculation based on previous data by using the same model and was centered on the primary outcome measure: the change from baseline in total nasal symptoms after antigen challenges compared between treatments. We assumed that the score for nasal symptoms would be reduced by 1.5 with active treatment and that the standard deviation of the measurement would be 3. When assuming $p < 0.05$, a reduction of 1.5, and a population standard deviation of 3, then 20 subjects in each group would provide 80% power of detecting a significant difference.

RESULTS

Subjects

A total of 43 patients were initially screened. Twenty subjects entered and completed the study. The mean age of the subjects was 27.7 ± 3.8 years, and there were 9 men and 11 women. There were no adverse events to report.

TNSS

TNSS after diluent challenge were similar in both treatment groups (investigational product, median 0 [range, 0–9]; placebo, median 0 [range, 0–3]; $p = 0.73$). After challenges 1 and 2, there was a significant increase in symptom scores after allergen challenge in both treatment arms at both the 15-minute and 60-minute time points (Fig. 1). When the total change from the diluent response was compared for both challenges on both treatments, there were no significant reductions in TNSS after treatment with the investigational product compared with the treatment with placebo for both challenge 1 (investigational product, median 6.5 [range, –10

Figure 1. Total nasal symptom scores (TNSS). TNSS after allergen challenges are depicted. Challenge 1 examined the response 10 minutes after study drug or placebo administration, and challenge 2 evaluated the efficacy 2 hours after administration of the investigation product or placebo. The x-axis on the graphs represents the responses after diluent challenge and those 15 and 60 minutes after allergen challenges. Median values are depicted.

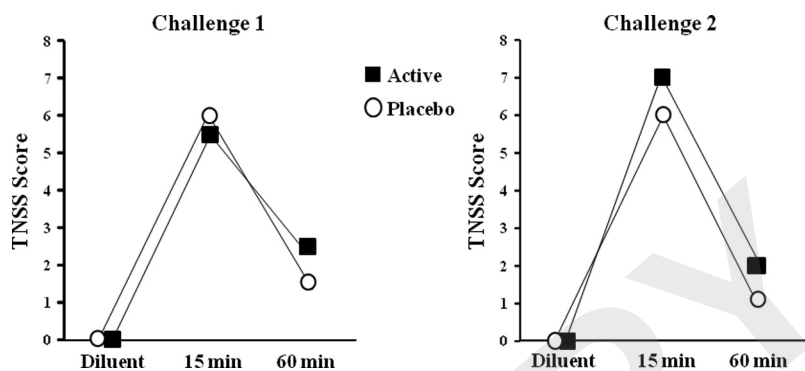


Figure 2. The total change from diluent challenge after the two time points in total nasal symptom scores (TNSS) is depicted here for challenges 1 and 2. Individual data are depicted with solid bars, which indicate median values.

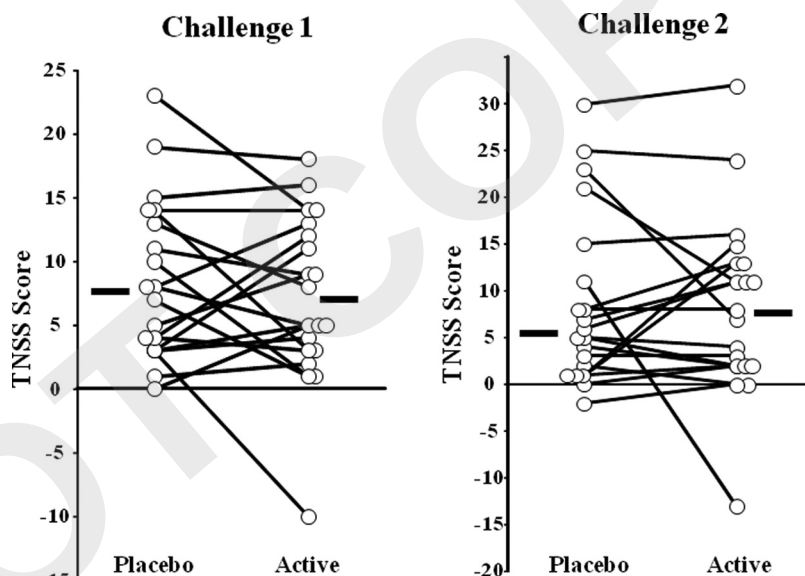
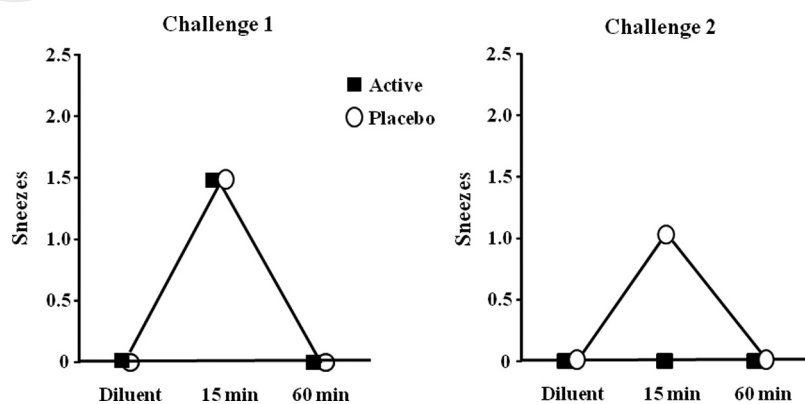


Figure 3. Sneezes. The number of sneezes after allergen challenges is depicted here. Challenge 1 examined the response 10 minutes after study drug or placebo administration, and challenge 2 evaluated the efficacy 2 hours after administration of investigational product or placebo. The x-axis on the graphs represents the responses after diluent challenge and those 15 and 60 minutes after allergen challenges. Median values are depicted.



to 18]; placebo, median 7.5 [range, 0–23]; $p = 0.43$) and challenge 2 (investigational product, median 7.5 [range, –13 to 32]; placebo, median 5.5 [range, –2 to 30]; $p = 0.74$) (Fig. 2).

Individual Nasal Symptom Scores

Individual symptoms showed findings similar to the TNSS scores, again, with no statistically significant differences between the treatments ($p > 0.05$, all comparisons).

Number of Sneezes

There was a significant increase in the number of sneezes 15 minutes after challenge 1 and challenge 2 for both treatments ($p <$

0.05), but there were no significant increases at the 60-minute time point (Fig. 3). When the change from diluent was compared between treatments, there were no significant differences for challenge 1 (investigational product, median 1.5 [range, –4 to 14]; placebo, median 2.0 [range, –8 to 11]; $p = 0.96$) and challenge 2 (investigational product, median 1.0 [range, –4 to 9]; placebo, median 1.0 [range, minus]6 to 5]; $p = 0.48$) (Fig. 4).

PNIF

The baseline PNIF was similar for both treatments ($p = 0.24$). There was a significant overall decrease in PNIF after allergen during challenge 1 after both treatments (investigational product,

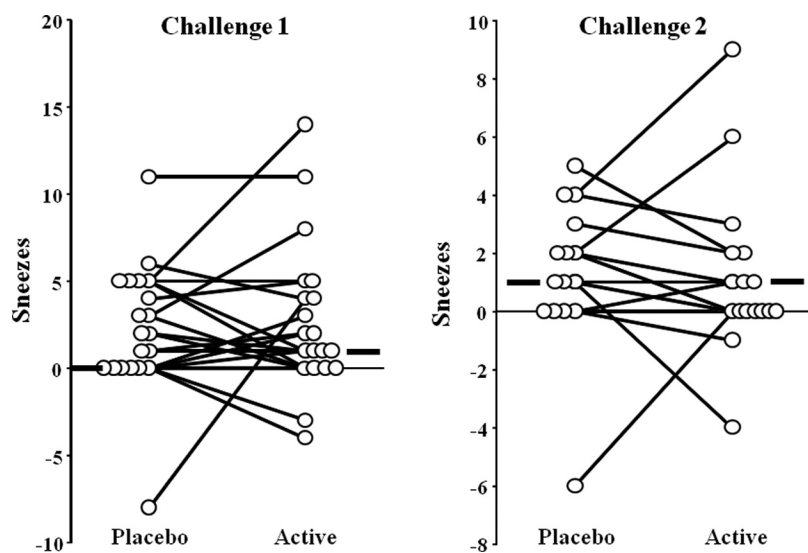


Figure 4. The total change from diluent challenge after the 2 time points in number of sneezes is depicted here for challenges 1 and 2. Individual data are depicted with solid bars, which indicate median values.

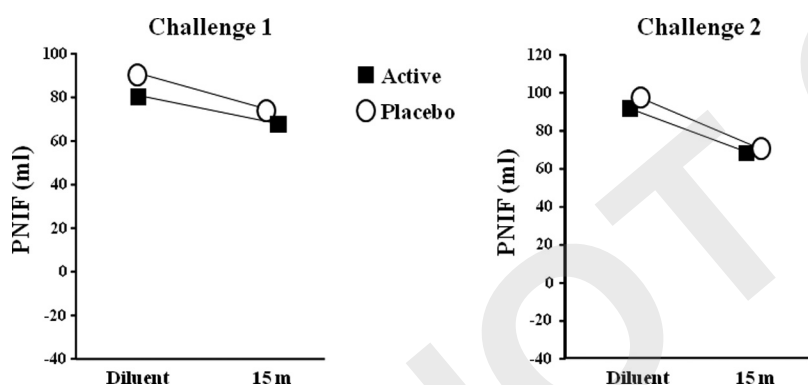


Figure 5. Peak nasal inspiratory flow (PNIF) after allergen challenges are depicted. Challenge 1 examined the response 10 minutes after investigational product or placebo administration, and challenge 2 evaluated the efficacy 2 hours after administration of the study drug or placebo. The x-axis on the graphs represents the responses after diluent challenge and those 15 minutes after allergen challenges. Median values are depicted.

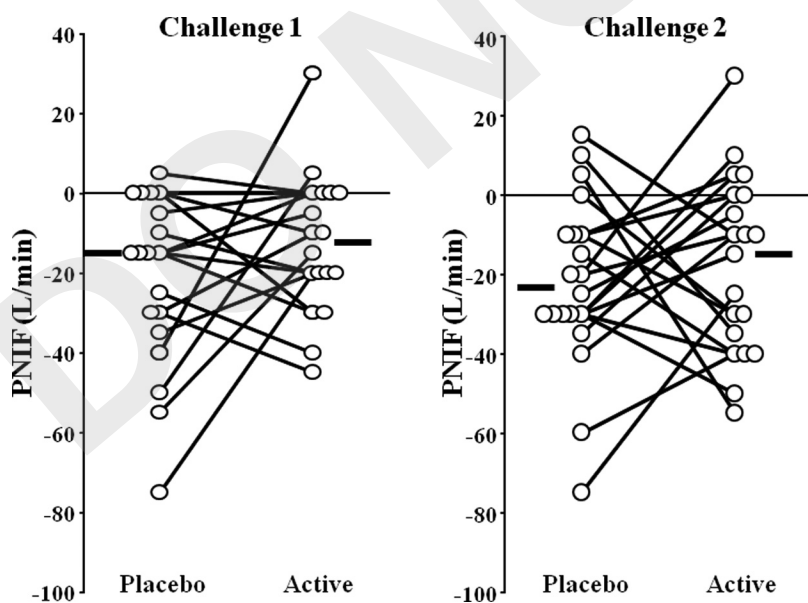


Figure 6. The total change from diluent challenge after the 15-minute time point in peak nasal inspiratory flow (PNIF) is depicted for challenges 1 and 2. Individual data are depicted with solid bars, which indicate median values.

$p = 0.005$; placebo, $p = 0.001$) (Fig. 5) but no significant differences between the treatments when change from diluent was analyzed (investigational product, median -12.5 L/min [range, -45 to 30 L/min]; placebo, median -15 L/min [range, -75 to 5 L/min]; $p = 0.31$) (Fig. 6). Similarly, at 2 hours, in challenge 2, there, again, was a significant overall decrease in PNIF after allergen challenge in both

treatment arms (investigational product, $p = 0.005$; placebo, $p = 0.001$) (Fig. 5) but no significant difference between the treatments when the change from diluent was analyzed (investigational product, median -12.5 L/min [range, -55 to 30 L/min]; placebo, median -22.5 L/min [range, -75 to 15 L/min]; $p = 0.51$) (Fig. 6).

CONCLUSION

As in many previous studies, nasal allergen challenge induced an allergic response characterized by an increase in sneezes and nasal symptoms, and a decrease in peak nasal airflow, an objective measure of nasal congestion. There was no significant inhibition of the allergic response by the allergen blocker at either 15 minutes or 2 hours after administration, which indicated that the allergen blocker was no more effective than placebo. Our study used nasal challenge model to evaluate the efficacy of this purported nasal allergen blocker, which was being developed for over-the-counter use. Testing efficacy is a novel approach for companies developing over-the-counter products because such treatments can be approved as a device (no interaction of the blocker with the nasal mucosa) without demonstration of efficacy.

Supplements such as omega-3 fatty acids, Quercetin, and Boswellia are sold over the counter under the premise that, by lowering inflammation, these will alleviate allergy symptoms and support the immune system as it manages allergens, although no data support this claim. Homeopathic therapy can be promoted with analogous claims. However, some alternative treatments can have their efficacy shown in clinical trials: certain local honey is thought to have some effect on allergy symptoms, given that pollen ingested in the honey may promote immune tolerance. Herbal supplements and even spices, such as ginger, cinnamon, turmeric, black pepper, pippali, and licorice, are all touted as providing ways to control allergies. Conversely, the elimination of certain foods from a patient's diet is suggested to decrease mucus production. (<http://www.mindbodygreen.com/0-8312/5-all-natural-allergy-treatments.html>) These supplements and other over-the-counter drugs promise a reduction of the allergic response. Widely found online, they are often advertised without U.S. Food and Drug Administration approval and promoted without proper investigation or clinical trials that might prove their effectiveness, efficacy, or safety, thus the consumer makes his or her choice based on labels.

The product investigated in this study was a nasal spray intended to limit airborne allergens from contacting the nasal mucosa and thereby decrease the severity of allergic rhinitis. In the effort to assess whether our investigational product worked and the duration of action of such an effect, the nasal spray was given before nasal allergen challenges, and the acute response was assessed at early and late time points. Unfortunately, we were not able to show a significant inhibitory effect of the product compared with placebo on any of the outcome measures.

Our results have allowed us to demonstrate that our study design worked properly, by clearly showing increases in symptoms after allergen challenges. In addition, we were able to show a significant decrease in PNIF in both treatment groups after allergen challenges. Although we were unable to conclusively demonstrate improvement

in patient symptoms, this study design might be used in the future for assessment of the efficacy of other allergy drugs or devices presumed to affect the immediate allergic reaction.

In nasal challenge studies of similar or smaller sizes, we were able to show the effectiveness of intranasal steroids and of oral and intranasal antihistamines.^{3,8} Based on the data generated in our study, we did a futility analysis, which showed that 894 subjects would be needed to show a statistical difference in the acute response immediately after challenge. Even more subjects ($n = 11,334$) would have been needed to show a positive response at 2 hours after administration of the investigational product. Thus, although one could argue that a large trial might have shown an effect, such an effect would be small and not meaningful clinically in comparison with these treatments, especially because antihistamines and intranasal steroids are already available over the counter. Our investigational product did not prove significantly better than placebo control in treating symptoms associated with seasonal allergic rhinitis. The lack of clinically meaningful results regarding the effectiveness of the experimental drug at improving symptoms led the sponsor (McNeil Consumer Healthcare, Fort Washington, PA) to cease further development of the device under study.

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